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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/578,077 | 05/08/2007 | Yoshio Miki | 08178.0031 | 3057 |

7590 02/19/2010

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| JOHANNSEN, DIANA B | |
| ART UNIT | PAPER NUMBER |
| 1634 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/19/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/578,077 | MIKI ET AL. | |
| | Examiner | Art Unit | |
| | Diana B. Johannsen | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 6-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0207; 1209*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *PTO-90C(Req for Information)*.

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| APPLICATION NO./ CONTROL NO. | FILING DATE | FIRST NAMED INVENTOR / PATENT IN REEXAMINATION | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 10578077 | 5/8/07 | MIKI ET AL. | 08178.0031 |

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| Diana B. . Johannsen | |
| **ART UNIT** | **PAPER** |
| 1634 | 20100213 |

**DATE MAILED:**

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner for Patents**

Requirement for information under 37 CFR 1.105.

1. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application.
2. As evidenced by the abstract of Isomura et al (Amer. J. Hum. Genet. 73(5):174, presented at the 53rd Annual Meeting of the American Society of Human Genetics 6 Nov 2003; cited in the IDS of February 2007), some inventors named in the present application, along with additional co-authors, made an oral presentation and/or poster presentation disclosing 2 SNPs found to be associated with granulocytopenia based on a study of 54 breast cancer patients treated with paclitaxel (see cited abstract) at a scientific meeting on November 6, 2003 (just less than one year prior to applicants' effective filing date of November 5, 2004). The inventive entity of the instant application differs from the authorship of the above-referenced abstract, and, as noted in the enclosed Office action, applicant has not established that the claimed invention was in fact disclosed in the foreign application of which the instant application claims benefit (and which has a filing date of November 5, 2003). As discussed in MPEP 2128.01, written copies of presentations such as that noted above may constitute "printed publications" qualifying as prior art if disseminated without restriction, and publically displayed documents can similarly constitute prior art if they have been made "publically accessible" at an event such as a scientific meeting.
3. Accordingly, in response to this requirement, please provide answers to each of the following interrogatories eliciting factual information, and provide copies of the materials requested in accordance with the instructions noted below:
a. Were any written copies of the presentation noted above disseminated without restriction? If replying in the affirmative to this interrogatory, please also provide a copy of the material distributed.
b. What documents were publically displayed at the Meeting referenced above (i.e., please provide a copy of any publically displayed materials)? Additionally, please provide a description of the manner and duration of the display sufficient to allow the examiner to determine whether the materials were publically accessible.
4. This information is being required because it is necessary for the examiner to review any materials as noted in 3 a) or b), above, in order to determine whether those materials constitute prior art under 35 USC 102(a) that must be applied against applicants' claims, and because it is not possible for the examiner to independently determine what materials may have been provided and/or displayed, and in what manner.
5. The fee and certification requirements of 37 CFR 1.97 are waived for those documents submitted in reply to this requirement. This waiver extends only to those documents within the scope of this requirement under 37 CFR 1.105 that are included in the applicant's first complete communication responding to this requirement. Any supplemental replies subsequent to the first communication responding to this requirement and any information disclosures beyond the scope of this requirement under 37 CFR 1.105 are subject to the fee and certification requirements of 37 CFR 1.97.

6. The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained may be accepted as a complete reply to the requirement for that item.
7. This requirement is an attachment of the enclosed Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action

/Dave Nguyen/
SPE, Art Unit 1634

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634

PTO-90C (Rev.04-03)

## DETAILED ACTION

1. This application is a 371 of PCT/JP04/16805, filed November 5, 2004. The International Search Report for the PCT application has been received and considered.

### *Priority and Requirement for Information*

2. **Applicant's attention is drawn to the Requirement for information under 37 CFR 1.105 enclosed herewith**. It is noted that the foreign priority papers filed in the present application cannot be relied upon because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

### *Election/Restrictions*

3. Applicant's election with traverse of Group I (claims 1-9) in the reply filed on October 28, 2009 is acknowledged. The traversal pertains to the restriction of Groups I-II, and is on the following ground(s). Applicant argues that the Reeve reference does not teach or suggest a kit embraced by the claims. The reply urges that Reeve does not teach kits for predicting granulocytopenia risk, and states that "Reeve does not disclose the genetic polymorphisms in the two genes CYP2C8 and BUB1b…let alone a kit for detecting these genetic polymorphisms." These arguments have been thoroughly considered but are not found persuasive. As was indicated in the Requirement of September 21, 2009, Reeve teaches kits meeting the requirements of the claims. The arrays present in the kits of Reeve could be used to detect the polymorphisms of the claims, and thus could in fact be used "for predicting the risk of the occurrence of

granulocytopenia caused by paclitaxel therapy in a subject." While the intended uses recited in applicant's claims are noted, these recitations are not accorded patentable weight when comparing the products of the claims with the prior art. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, it meets the claim. See also MPEP 2111.02. Accordingly, applicant's arguments are not persuasive.

The requirement is still deemed proper and is therefore made FINAL.

4. Applicant's election of the species of "a genetic polymorphism at the 11$^{th}$ nucleotide of the sequence defined by SEQ ID NO: 6 in" BUB1b gene in the reply filed on October 28, 2009 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It is noted that applicant identified claims 1 and 4-9 as reading on the elected species. However, claims 6-9 require identifying combinations of polymorphisms in different genes (and thus are directed to separate species than that elected by applicant; see the requirement of September 21, 2009, paragraphs 3-5). Accordingly, **the claims reading on the elected invention are claims 1 and 4-5**.

5. Claims 2-3 and 6-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and non-elected

species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 28, 2009.

***Oath/Declaration***

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

7. As a new oath or declaration is required, it is also **suggested** that applicant modify the oath/declaration to properly identify the instant application as the national stage of PCT/JP04/16805 (rather than including an improper priority claim under 35 USC 120 to the PCT application). However, it is noted that correction of this error is not required, as the status of the application as a 371 of PCT/JP04/16805 is considered to be clear (based on acceptance of the application under 35 USC 371; see Form PCT/DO/EO/903 mailed July 9, 2007).

***Specification***

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., page 14). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code; it is noted that this can be accomplished by simply deleting the recitation “http://”. See MPEP § 608.01.

***Claim Rejections - 35 USC § 112, second paragraph***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 and 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: any step actually related to predicting granulocytopenia risk. The claim is drawn to a method "for predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject." However, the only method step of the claim requires identifying one or more polymorphisms; there is no indication as to how (or even whether) this relates to predicting risk. Accordingly, the claim appears to lack a step essential to the practice of the claimed method. It is noted that dependent claims 4-5 are excluded from this rejection because those claims indicate how risk is assessed/predicted.

Claims 4-5 are indefinite over the recitation of the language "where the gene isolated from the subject is….the genotype at the 11$^{th}$ nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b gene is A/A". This language is confusing, as it is not clear whether this claim language actually further limits the properties of the "gene" being isolated, whether this language in fact requires identification of a particular genotype in the molecule being isolated, etc. It is not

clear how a "gene" may actually be a "genotype"; thus, the meaning of this claim language is unclear. Clarification is required.

***Claim Rejections - 35 USC § 112, first paragraph***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is again noted that it is not clear how the method of claim 1 actually relates to prediction of risk. However, as the claim includes an intended use "for predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject," enablement of the claim must be considered with respect to this intended use. This rejection applies to claim 1 to the extent that the claim is drawn to a method in which risk of granulocytopenia is predicted (as occurs in dependent claims 4-5)(as opposed to a method merely requiring identification of a polymorphism).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the

claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)). It is noted that the examiner has considered all of the evidence related to each of these factors, and that those factors, reasons and evidence that have led to a conclusion that enablement is lacking are discussed below (*MPEP* 2164.04).

The species elected for examination is "a genetic polymorphism at the 11$^{th}$ nucleotide of the sequence defined by SEQ ID NO: 6 in" BUB1b gene. Claims 1 and 4-5 are drawn to methods "for predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject" comprising a step of "identifying" the elected polymorphism "in a gene isolated from the subject. Dependent claim 4 further requires that risk "is predicted to be high in the case where the gene isolated from the subject is…the genotype at the 11$^{th}$ nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b gene is A/A," while dependent claim 5 further requires that the "risk is predicted to be low" when the same gene/genotype is instead A/G or G/G.

The specification discloses screening a single group of 54 breast cancer patients (stage II or IIIa, age 70 or younger; receiving paclitaxel therapy preoperatively and prior to radiation or other chemotherapy) to identify SNPs associated with "adverse side effects" resulting from paclitaxel therapy, including

granulocytopenia (see Examples at pages 26-33). Applicants report a significant association between granulocytopenia and an A/A genotype at the position in BUB1b corresponding to nucleotide 11 of instant SEQ ID NO: 6 (see, e.g., Table 13), and teach that the SNP had the highest correlation of those screened in the BUB1b gene ($p = 0.0062$, odds ratio 5.11). Applicants also conclude that "the potential for the occurrence of granulocytopenia can be reliably predicted by using" this SNP in combination with a CYP2C8 gene SNP also exhibiting a significant correlation with granulocytopenia in the studied population of 54 patients. In view of the guidance in the specification, an ordinary artisan would recognize that applicants have identified a possible association between the elected SNP and granulocytopenia following paclitaxel therapy in human subjects. However, such an artisan would also readily recognize, based on the data and information provided in the specification, that applicants' findings have yet to be replicated and were obtained using an extremely small sample of patients. Further, one of skill in the art would be aware of the high degree of unpredictability in the relevant art. For example, Ioannidis et al (The Lancet 361:567-571 [Feb 2003]) disclose a large number of comparisons of genetic associations in large versus small studies, and report that studies of large and small studies often produce significantly different conclusions regarding genetic associations (see entire reference), and further that "only 16% of genetic associations identified were subsequently replicated with formal statistical significance, without heterogeneity or bias" (page 570, right column). Thus, Ioannidis et al establish that caution is necessary in interpreting preliminary,

unreplicated data, particularly when obtained using a small population. Similarly, Dahlman et al (Nature Genetics 30:149-150 [Feb 2002]) disclose that "true genetic associations" typically require the analysis of thousands of subjects, and that initial findings from genetic association studies must be replicated before a skilled artisan would consider such findings to be valid (see entire reference). Thus, given the state of the art at the time the instant invention was made and the well-known unpredictability of the art with respect to genetic association studies at that time, a skilled artisan would have recognized a need for further enabling guidance with regard to the successful practice of the claimed invention. Lacking such guidance from the specification, one of skill in the art may look to the teachings of the prior art. However, in the present case, the prior art is silent with respect to any association between the elected polymorphism and risk of granulocytopenia or other side effects following paclitaxel treatment (either in human or any other type of subjects). The prior art as exemplified by the dbSNP entry for rs2277559, particularly, the portion of that entry set forth in ss3214454 (Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda (MD): National Center for Biotechnology Information, National Library of Medicine. dbSNP accession: **rs2277559** and **ss3214454** (Build 100, publicly available 24 Oct 2001)(Available from: http://www.ncbi.nlm.nih.gov/SNP/)) discloses the existence of the elected polymorphism and the detection thereof, but is silent regard any risk associations. Thus, the prior art cannot be relied upon in the present case with regard to enablement of methods for "predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy". Given the high

skill level of one skilled in the art, it is clearly within the ability of such an artisan to conduct further experimentation aimed at determining whether the association reported by applicant (which association must exist in order for the claimed invention to function as required) can be replicated, and constitutes a true genetic association. However, the outcome of such experimentation is completely unknown and unpredictable, and it is entirely possible that even an infinite quantity of experimentation would be insufficient to enable the claimed invention. The prior art teachings of Ioannidis et al and Dahlman et al indicate that initial reports of genetic associations are very often never replicated, and that such replication is required before such associations can be considered "true" and reliable. As applicants' data does not meet this minimum threshold, such that no true association between the elected polymorphism and granulocytopenia risk has as yet been established, it would clearly require undue experimentation to use applicants' claimed invention.

***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by the dbSNP entry for rs2277559, particularly, the portion of that entry set forth in ss3214454 (Database of Single Nucleotide Polymorphisms (dbSNP). Bethesda

(MD): National Center for Biotechnology Information, National Library of Medicine. dbSNP accession: **rs2277559** and **ss3214454** (Build 100, publicly available 24 Oct 2001). Available from: http://www.ncbi.nlm.nih.gov/SNP/).

It is again noted that claim 1 as written does not appear to require any step(s) requiring or resulting in prediction of granulocytopenia risk; rather, the only actual method step set forth in the claim merely requires "identifying in a gene isolated from" a subject the elected polymorphism "at the 11$^{th}$ nucleotide of the sequence defined by SEQ ID NO: 6 in BUB1b".

dbSNP entry rs2277559 sets forth SEQ ID NO: 6 (note the centrally located polymorphism and 10 nucleotides of flanking sequence on each side, which sequence corresponds to SEQ ID NO: 6). The first entry for rs2277559, ss3214454, also sets forth this sequence (see submission report for ss3214454, enclosed herewith as part of a larger printout of the dbSNP entry for rs2277559). The "Method Detail" for ss3214454 (provided on the last page of the printout) discloses that the polymorphism was identified by amplification of human genomic DNA and direct sequencing of amplified PCR products, such that identification of the polymorphism in a gene isolated from a subject is disclosed. Accordingly, the dbSNP entry for ss3214454 (publicly available in Build 100, 24 Oct 2001) anticipates the claimed invention. While the recitation in the preamble of the intended use "for predicting the risk of the occurrence of granulocytopenia caused by paclitaxel therapy in a subject" is noted, MPEP 2111.02 states that:

> If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition

> of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction. *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999).

Further, a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). In the instant case, the claim requires a single step of identifying a polymorphism and includes no actual method steps that relate to risk prediction. There is no manipulative difference between applicants' claimed method and that of the prior art, such that the recitation "for predicting the risk…" is considered to constitute an intended use that is non-limiting for purposes of comparing the claimed invention to the prior art.

## ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634